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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 09/855,587 | 05/16/2001 | Yoshiki Sasai | 00766.000044. | 1416 |

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| EXAMINER | |
|---|---|
| SGAGIAS, MAGDALENE K | |
| ART UNIT | PAPER NUMBER |
| 1632 | |
| MAIL DATE | DELIVERY MODE |
| 11/05/2010 | PAPER |

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Advisory Action Before the Filing of an Appeal Brief | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/855,587 | SASAI ET AL. | |
| | Examiner | Art Unit | |
| | MAGDALENE SGAGIAS | 1632 | |

**--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --**

THE REPLY FILED 20 October 2010 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☒ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:

a) ☒ The period for reply expires *4* months from the mailing date of the final rejection.

b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☐ The Notice of Appeal was filed on _____. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☐ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
   (a) ☐ They raise new issues that would require further consideration and/or search (see NOTE below);
   (b) ☐ They raise the issue of new matter (see NOTE below);
   (c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
   (d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: _____. (See 37 CFR 1.116 and 41.33(a)).

4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).

5. ☐ Applicant's reply has overcome the following rejection(s): _____.

6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).

7. ☒ For purposes of appeal, the proposed amendment(s): a) ☐ will not be entered, or b) ☒ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.
   The status of the claim(s) is (or will be) as follows:
   Claim(s) allowed: _____.
   Claim(s) objected to: _____.
   Claim(s) rejected: *1, 18-21, 23-24, 74-75, 80-90*.
   Claim(s) withdrawn from consideration: _____.

AFFIDAVIT OR OTHER EVIDENCE

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).

9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).

10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: See Continuation Sheet.

12. ☐ Note the attached Information *Disclosure Statement*(s). (PTO/SB/08) Paper No(s). _____

13. ☐ Other: _____.

/Anne-Marie Falk/
Primary Examiner, Art Unit 1632

Continuation of 11. does NOT place the application in condition for allowance because: Applicants have not provided guidance to overcome the rejections of record.

A. The rejection of claims 1, 18-21, 23-24, 74-75, 80-90 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement is maintained for the reasons of record in the office action dated 06/24/2010.
Applicants argue claim 81 has been amended to address the Examiner's concerns. As to the remaining points: a) Examples 1 and 14 show culturing embryonic stem cells in vitro, b) the specification page 45, lines 1-5 explicitly teaches it is preferable that retinoic acid is not used. Moreover, although the Examiner points out that the feature "in the absence of retinoic acid" is not supported by Examples 1 and 14 such is untrue. Examples 1 and 14 do not utilize retinoic acid in Examples 1 and 14, c) cells that are positive for dopaminergic neuron marker, cholinergic neuron marker, GABAergic neuron marker and serotonergic neuron marker (as recited in claim 80) were obtained by Example 1. Examples 10 and 11 evidence that such dopaminergic neuron can function as neuron, d) stem cells that are stained by anti-nestin antibody (as recited in claim 81) are obtained by Example 1. Specification page 23, lines 23-29 confirm that neural stem cells can be confirmed by staining by anti-nestin antibody. Applicant's arguments have been fully considered but they are not persuasive.

In response, regarding example 1 the specification describes the differentiation of embryonic stem cell into dopaminergic neuron however, it does not overcome the issue of not describing culturing an embryonic stem in the absence of retinoic acid resulting in a neural crest marker or a neural tube marker as required in the currently amended claim 1 or producing a dopaminergic neuron, an acetylcholinergic neuron, a 7-aminobutyratergic neuron or a serotonergic neuron, as required in the amended claim 80 or producing a neural stem cell which is stained by an anti-nestin antibody as required in the amended claim 81, because the examiner cannot find literal support for the absence of retinoic acid in example 1.
Regarding the example 14 the specification describes the differentiation induction of embryonic stem cell into various neural cells along the dorso-ventral axis however, for the same reasons as discussed for example 1 there is no description for culturing the ESCs in the absence of retinoic acid resulting in the differentiated cells as instantly claimed in the currently amended claims for the same reasons of record in the office action dated 06/24/2010, pages 2-4).
Regarding examples 10 and 11 again there is no description of a culture in the absence of retinoic acid as discussed for examples 1 and 14. The issue is not the staining of cells by ant-nestin antibody but the issue is for culturing the ESCs in the absence of retinoic acid as required in the instant invention. Therefore, the rejection is maintained because literal support for the method steps in the absence of retinoic acid and what is accomplished by these steps cannot be found in the specification for culturing in the absence of retinoic acid as instantly claimed.

B. Claims 1, 18-21, 23-24, 25-73, 80-90 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for culturing a mouse embryonic stem cell in vitro in the presence of a stroma cell without forming embryoid body, wherein the stroma cell OP9 cell or PA6 cell, does not reasonably provide enablement for culturing a human embryonic stem cell in vitro in the presence of a stroma cell without forming embryoid body, wherein the stroma cell OP9 cell or PA6 cell, and wherein the embryonic stem cell is selected from the group consisting of (b) an embryonic stem cell established by culturing an early embryo produced by nuclear transplantation of the nucleus of a somatic cell; and (c) an embryonic stem cell in which a gene on the chromosome of the embryonic stem cell of (b) is modified using gene engineering is maintained for the reasons of record in the office action dated 06/24/2010 pages 4-9..
Applicants argue according to the Examiner, the conditions applicable for controlling the differentiation of mouse embryonic stem cells are not applicable to human embryonic stem cells. Applicants argue this is a repeat of a previously-withdrawn rejection. In this regard, the Examiner may recall that in the Office Action dated January 16, 2003, it was asserted only treating mouse ES cells was enabled. In response, Applicants submitted PNAS, Vol. 99 (2002) 1580 and pointed out that even in monkey ES cells, differentiation of dopaminergic neuron is induced by the method of the present invention. If the Examiner is now aware of information why such showing is irrelevant, she is respectfully requested to provide a suitable affidavit under MPEP §2144.03. Applicant's argument's have been fully considered but are not persuasive.

In response, the examiner is not able to locate on record Applicant's submittion of a PNAS, Vol. 99 (2002) 1580 reference regarding culturing monkey ES cells, differentiation of dopaminergic neuron is induced by the method of the present invention. If so Applicants should submit such reference paper. In addition, the examiner is not able to find such PNAS reference in the specification or IDS. However, the examiner has reviewed said PNAS paper (PNAS, 99(3): 1580-1585, 2002), which is Applicant's own paper and there is no teaching of culturing primate ES cel in the absence of retinoic acid. Therefore, the rejection is maintained because Applicants have not overcome the enablement issues with regard to human ES cells.

C. Lastly, Applicant's argue that to the extent the Examiner may be no longer persuaded by this argument, Cell, Vol. 131, No. 5 (2007) 861-72 (copy attached) shows the method of the present invention can be applied to human ES cells. See the first sentence in right column on page 864 ("human iPS cells could be induced by reported methods for hES cells") followed by description of the experiment doing so (page 864, fight column, line 3, et seq. and Figure 6). Applicant's arguments have been fully considered but are not persuasive.
In response, the above cited reference teaches the retinoic acid is required for during neuroectoderm induction for motorneuron specification and suggest that the stem cells have restricted capacity to generate region-specific projection neurons even at the early developmental stage (see abstract). Inedited the above reference teaches that functional motoneurons can be efficiently generated from hES cells through induction of neuroectoderm, specification and/or caudalization by retinoic acid during the late phase of neuralization, and subsequent differentiation to postmitotic motoneurons in the presence of the ventralizing morphogen SHH. By dissecting the process of neuroectodermal differentiation, we have discovered that specification of early-born projection neurons such as spinal

motoneurons requires treatment with morphogens like retinoic acid before precursors become Sox1-expressing neuroectodermal cells (see p 219, 1st column, 2nd paragraph). Therefore, the rejection is maintained because Applicants have not overcome the enablement issues with regard to human ES cells.

D. The rejection of claims 1, 23, 81, 82-87 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nakano et al, (Science, 265: 1090-1101, 1994) in view of Samarut et al (US 6,114,168) is withdrawn in view of the amendment to claims 1,80, 81 for culturing under serum free conditions. Nakano and Samarut teach culturing under serum conditions